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(54) CONTROL AND REGULATION DEVICE FOR GLYCEMIA

(71) We, ASSOCIATION POUR LA RECHERCHE ET LE DEVELOPPEMENT DES METHODES ET PROCESSUS INDUSTRIELS A.R.M.I.N.E.S. a research Association organised according to the laws of France, of 60, Boulevard Saint-Michel, 75006 PARIS (France), do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:-

The present invention relates to the control and regulation of glycemia (that is the glucose rate in the blood) of diabetic patients.

It is known that the glucose rate in blood is normally of the order of one gram for human beings and that this rate is maintained in the vicinity of this value, in a healthy person, by an auto-regulation system comprising the liver, the pancreas, the hypophysis and other organs.

With diabetic patients, the glycemia is usually above 2 grams (hyper-glycemia) and this rate is reduced by means of insulin the effect of which is to reduce the glucose rate. However, said rate should not fall below 0.8 gram since in this case there would be a hypo-glycemia.

It is therefore important to maintain the glycemia of diabetic patients dependent on insulin at a value nearing 1 gram and preferably between 0.8 and 1.2 g.

The device according to the invention aims at actually providing control and regulation of glycemia in order to maintain it in the vicinity of 1 g.

The device according to the invention comprises, in combination, means for continuously withdrawing and sampling a flux of the blood of the diabetic patient, measuring means for continuously determining the glucose rate in said flux, electronic regulation means for comparing the rates thus determined with the glucose rate of a normal healthy person and for determining the quantity and type of product capable of adjusting the glucose rate required to bring back the glucose rate of the patient to the normal rate, and means controlled by said electronic regulation means for injecting said product in the quantity so determined into the patient.

Optionally, the device also includes visual display means for the glucose rate determined by said measuring means and/or alarm means capable of operating when the difference between said rate and the normal rate is in excess of a threshold level and/or when an operation anomaly occurs.

Preferably, the device comprises also means for determining the red corpuscle concentration of the blood flux sampled from the patient.

In any case, the invention will become more apparent from the following description as well as from the accompanying drawings, said description and drawings being of course given mainly by way of exemplification. In the drawings:-

Figure 1 shows schematically a device according to the invention controlling a diabetic patient;

Figure 2 illustrates one of the elements of the device of Figure 1, namely the apparatus for determining the red corpuscle concentration in the blood flux sampled from the diabetic patient;

Figure 3 illustrates schematically the regulation chain of the device of Figure 1 which comprises said electronic regulation means; and

Figure 4 shows in block-form the electronic unit receiving the measuring signals and controlling the injection, visual display and alarm means in cooperation with a computing

unit.

One form of complete unit according to the invention is illustrated in Figure 1 in which the pipes transporting liquids are represented in double lines with the flow direction indicated by arrows, whereas the electric leads carrying information are shown in single lines, the arrows indicating the circulation direction of the electric data.

Whole blood from a diabetic patient 2 dependent on insulin is sampled by means of a pump 1, for instance of the roller type. Pump 1 also continuously sucks a certain quantity of heparin contained in a container 3. Figure 1 shows pipe 5 for heparin and pipe 4 for the whole blood which is mixed with the heparin at the point of insertion of the sampling catheter 6 which is of the double light type. Heparin is an anticoagulant substance the presence of which in the blood avoids coagulation of the latter. Coagulation could result in the obstruction of the pipes and distortion of the measurements.

From pump 1, the heparined whole blood is transferred by a pipe 7 into a device 8 for measuring the red corpuscle content and comprising, for instance, an hematocrit electrode which will be described in more detail with reference to Figure 2. Said electrode continuously measures the red corpuscle content of the blood and heparin mixture which should normally contain a constant proportion of heparin. However, when the elements of the device described so far and indicated by reference numerals 1, 3, 4, 5, 6 and 7 do not operate correctly, the heparin percentage may be modified, and this would lead to errors in the determination of the glycemia in unit 9 which is a glucose analyser. Since the corpuscle concentration in blood is practically invariable in the human system over a long period, its determination in the hematocrit electrode 8 allows detection of a modification of the heparin rate in the blood carried by pipe 7. In fact, if the heparin rate is constant, the quantity of red blood corpuscles determined by electrode 8 should be constant. When there is a variation in this quantity of red corpuscles, an anomaly has occured; said anomaly may be a modification of the heparin rate, arising as hereabove mentioned, or from the presence of air bubbles which result in the formation of a blood clot from a leak in one of the pipes.

Downstream of the hematocrit electrode 8 is disposed, as previously mentioned, a glucose analyser 9 which need not be decribed in detail since it is of known type. It can operate either through a chemical and colorimetric route, or through a electro-chemical route. It is also possible to determine the glucose rate in the blood mixed with heparin by using other properties such as for instance optical properties.

In any case, and whatever the type of the glucose analyser used, the latter emits an electric signal (voltage or current) which is a function of glycemia.

After passing through the glucose analyser 9, the blood mixed with heparin is collected in a vessel 10.

The signal from the glucose analyser 9, as well as the signal transmitted by the hematocrit electrode 8 which is a function of the quantity of red corpuscles in the blood is transmitted to an electronic unit 11 which will be described hereafter with reference to Figure 4 and which will be called hereafter the glucostat since it represents the main element for the regulation of the glucose content in the blood of patient 2.

Glucostat 11 is associated with a computing unit 12 which may be for instance a digital computing unit of the type manufactured and sold by the HEWLETT-PACKARD Company under number HP 9815 A, or a programmable computer or computing unit of equivalent or higher performance to that of the HP 9815 A. The computing unit controls a printer 13 which prints the regulation important parameters: glucose content in the blood of patient 2, insulin rate injected to the patient, glucose or glucagon rate injected to the patient and optionally the quantity of red blood corpuscles. A further display means is constituted by a tracing table with several routes 14 operated by glucostat 11.

The glucostat 14 which comprises also an optical electronic display system for the glucose content in the blood of patient 2, controls the regulation of the glucose rate by actuating, according to the results from the glucose analyser 9, either of the two pumps 15 and 16. Pump 15 is provided for injecting insulin (thereby reducing the glucose rate) to patient 2 from an insulin container 17 via a pipe 18, whereas pump 16 is provided for injecting glucose (which of course is capable of increasing the blood glucose rate) to the patient from a glucose container 19 via a pipe 20, the insulin or glucose injection being made through a pipe 21. Glucagon may be used instead of glucose.

Briefly, if the quantity of red blood corpuscles is normal, the glucostat 11 operates as follows:

a) when the glucose analyser 9 indicates a normal glycemia, glucostat 11 acts only on the insulin pump 15 by sending to the patient a very low quantity of this hormone (in a quantity called basal quantity);

b) when the glucose analyser 9 indicates a glycemia above normal, glucostat 11 starts pump 15 which transfers insulin to the patient via pipes 18 and 21;

c) when the glucose analyser 9 indicates a glycemia which is too low, glucostat 11

operates pump 16 for transferring to the patient glucose or glucagon via pipes 20 and 21.

The operation of glucostat 11 is described in more detail with reference to Figure 4.

Referring now to Figure 2, one form of apparatus for determining the quantity of red corpuscles in the blood and comprising a hematocrit electrode will now be described.

The apparatus of Figure 2 comprises a plurality of metallic pipes 22 which are joined end to end between plastic pipes 23 and larger diameter. Blood S mixed with heparin arrives from the left hand side via pipe 7 and flows away on the right hand side via pipe 24 (also represented in Figure 1) to the glucose analyser 9.

An input alternating voltage, for instance of 20 volts with a frequency of 500 Hertz, is applied at 25 between the two end metallic pipes across high value resistors 26 (with a rated value equal to or higher than 10 MΩ). The output signal which is a function of the quantity of red corpuscles in the blood flux S mixed with heparin is available at 27 and is sent to the glucostat 11. It will be remarked that a symetrical mounting is used in order to take precautions against noises induced by radiations from the feed network connected at 25. Induced voltages more or less identical in amplitude and phase will thereby be obtained at 28 and 29. By providing a differential system at the output of 27, a resultant amplified voltage without a component due to the network induction will be obtained.

The determination of the quantity of red corpuscles is based on the following considerations:

If ρh is the impedance of a liquid with red blood corpuscles and ρsh the impedance of the same liquid without red blood corpuscles, one has the equation:

$$\rho H = \rho SH \frac{\gamma + h}{\gamma(1-h)}$$

where γ is a parameter depending on the shape of the red blood corpuscles (which will be here considered as equal to 1.32) whereas h is the concentration of the red corpuscles (between 0.45 and 0.50 for blood).

If the resistances R are high relative to the resistance of the liquid, the circuit behaves as a steady current generator and

$$V^z = Vo \frac{\gamma + h}{\gamma(1-h)}$$

where Vz is the voltage V measured in presence of blood and Vo the voltage V measured in presence of a physiological liquid without red corpuscles.

The value of h will be obtained from this formula, and therefore the volumic percentage of the blood in the blood + heparin mixture.

Figure 3 illustrates schematically the regulation chain formed substantially by elements 9, 11, 12, 15 and 16 of Figure 1. In this Figure block A shows the assembly of elements 11 and 12 of Figure 1, and block B shows pumps 15 and 16 of Figure 1; the patient is there again shown at 2 and the glucose analyser at 9.

In Figure 3, the various electric signals have also been indicated, viz. those representing:

- Gc : the desired value for the glycemia (rated point) from the computing device;
- G(t) : measured value of the glycemia from analyser 9;
- e(t) : value which is a function of the difference between Gc and G(t);
- $R_i(t) = f[e(t)]$: insulin rate to be injected;
- $R_d(t) = g[e(t)]$: glucose rate to be injected.

The servo-control of glycemia is provided entirely automatically. Due to a calculation and management program, specially written to this effect, the computing device 12 determines values (f[e(t)] and g[e(t)] from the measured values of glycemia. Functions f and g are empiric; they are based essentially on the observation of diabetes and of diabetic patients treated with insulin.

The program provides also control of the exchange of data between the computing device, some peripheral equipments and the glucostat.

Finally, there will be described with reference to Figure 4 the glucostat 11 which provides a number of functions, viz.

the amplification, filtration and analog/digital (that is numeric) conversion of the electric data from the various captors (glucose analysers and hematocrit electrode);

the control of the pumps;
the control of the glycemia display;
the control of an alarm indicating an abnormal operation of the device.

The glucostat has a quartz time base used as clock for the whole system, manages the data exchanges with the computing unit and provides finally the supply of alternating current at 500 Hz to the hematocrit electrode (other frequencies could also be chosen).

Referring to Figure 4, one sees that the glucostat comprises first a demultiplexor 30 directing towards the various units the data transmitted by the computing unit 12, said data being stored in the following units:

31, making the choice of the glucose analyser 9a, 9b;
32, making the gain choice of the differential amplifier 33;
34, making the choice of the type of measurement to be transmitted;
35, which stores the instructions for the insulin pump (shown at 15 in Figure 1);
36 which stores the instructions for the glucose pump (shown at 16 in Figure 1);
37, which stores the glycemia with a view to providing the display, and
38, which stores the eventual necessity of an alarm.

The glucostat comprises a time base 39 transmitting signals to a number of units, particularly to the computing device 12 via line 40 and to a generator 41 of sinusoidal voltage at 500 Hz through line 42, the time base 39 transmits rectangular signals at 500 Hz which are converted by generator 41 into a sinusoidal signal of same frequency). Said generator at 500 Hz supplies the hematocrit electrode 8 (at 25 in Figure 2). Said electrode transmits its information signal to a differential amplifier 43 adjusted on 500 Hz and followed by a rectifier (not shown) supplying a continuous voltage from the 500 Hz signal from the hematocrit electrode, said voltage being applied to an analogous multiplexor 27 whose function will be explained hereafter.

In Figure 4 an arrangement is shown in which several analysers of different types for the glucose rate, viz. 9a and 9b, are used. Unit 31 makes the choice of the analyser (9a or 9b) by means of an analogous multiplexor 44 which is also used as impedance adaptor for each of the glucose analysors and which selects one of the signals from 9a and 9b in order to transmit it to the aforementioned differential amplifier 33 the gain of which is determined by unit 32 as a function of the analyser type for the glucose, said gain being determined by the computing unit 12.

The analogous multiplexor 27 choses, under the control of unit 34, the glycemia signal (from 33) or the red corpuscle quantity (from 43) to be fed to the analog/digital converter 45 which is connected bi-laterally to the computing unit 12 to which it feeds a signal indicating either the glucose rate or the red corpuscle quantity of the blood mixed with heparin. As a function of the glucose rate and optionally of the red corpuscle quantity, the computing unit controls, through the demultiplexor 30 and the storage units 35 and 36, unit 46 providing control of the insulin and glucose pumps 15 and 16 respectively, through power circuits 47 and 48 respectively. The type of information transmitted by the computing unit 12 to unit 46 and from there to units 47 and 48 depends on the nature of the pumps 15 and 16 which are used: in the case of roller pumps, the signal represents the duration of the operation per time unit or the rotation speed of the pump, whereas for pulse pumps, the signal represents the number of strokes per minute.

Finally, the storing units 37 and 38 act respectively on a digital display device 49 and on a power amplifier 50 emitting through a loud-speaker positioned at 51 and transmitting a loud signal when the alarm threshold for the glucose content of the blood of patient 2 is exceeded and/or when an anomaly is detected (it may be an incorrect red corpuscle rate or a variation of the glycemia which is not physiologically compatible).

A device of the invention provides a very efficient control and regulation of the glycemiaa for diabetic patients dependent on insulin.

With such a device, one can maintain said glycemia between 0.8 and 1.2 grams, which is very satisfactory.

The operation of the device according to the invention is completely automatic and requires no continuous supervision since it supplies on the one hand a continuous record of the glycemia and on the other hand a loud signal when a dangerous threshold for the glycemia is exceeded, viz. when the difference e(t) between the value measured for the glycemia G(t) and the desired value for the glycemia Gc exceeds a predetermined alarm threshold and/or when there is an abnormal operation.

Instead of a loud alarm signal, one could foresee a luminous alarm signal, but such a signal requires a more careful supervision although it is possible to concentrate in a single room the alarm luminous signals from many devices according to the invention which control several diabetic patients.

WHAT WE CLAIM IS:

1. A control and regulation device for continuously monitoring glycemia for a diabetic

patient, comprising in combination, means for continuously withdrawing and sampling a flux of the blood of the diabetic patient, measuring means for continuously determining the glucose rate in said flux, electronic regulation means for comparing the rates thus determined with the glucose rate of a normal healthy person and for determining the quantity and type of product capable of adjusting the glucose rate required to bring back the glucose rate of the patient to the normal rate, and means controlled by said electronic regulation means for injecting said product in the quantity so determined into the patient.

2. A device according to claim 1, which also comprises means for determining the red corpuscle concentration of the blood flux sampled from the patient.

3. A device according to claim 2 wherein the means for determining the red corpuscle concentration comprises a hematocrit electrode comprising four metallic tubes arranged coaxially in series and separated by plastics tubes which are also coaxial with each other and with the metallic tubes means for applying an alternating voltage between the two metallic tubes at the end of the series and means for taking up an output voltage between the two inner tubes, said voltage being representative of the red corpuscle concentration.

4. A device according to claim 2 or claim 3, wherein said electronic regulation means receive a signal from said means for determining the red corpuscle concentration.

5. A device according to any one of the preceding claims, wherein the electronic regulation means comprise, in combination with a computing unit, a demultiplexor capable of transmitting selectively the signals from the computing unit, a series of storing units receiving the signals from the computing unit through said demultiplexor, and an analog/digital converter, means for selectively transmitting the output signal from said measuring means for determining the glucose rate, and, when present, the output signal from said means for determining the red corpuscle concentration, on said analog/digital converter, said analog/digital converter being in bi-lateral relation with the computing unit, a time base capable of controlling the timing of the various operations, optionally a sinusoidal voltage generator for said hematocrit electrode (when present) and, means for controlling said means for injection of the glucose rate adjusting product.

6. A device according to any one of the preceding claims which also includes visual display means for displaying the glucose rate of the patient as determined by the measuring means.

7. A device according to any one of the preceding claims which also includes alarm means arranged to operate when the difference between the measured glucose rate and the normal rate exceeds a threshold level and/or an operation anomaly occurs.

8. A device according to claim 7, wherein the alarm is an audible alarm.

9. A device for control and regulation of glycemia for a diabetic patient substantially as described herein with reference to and as shown in the drawings.

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Fig.1.

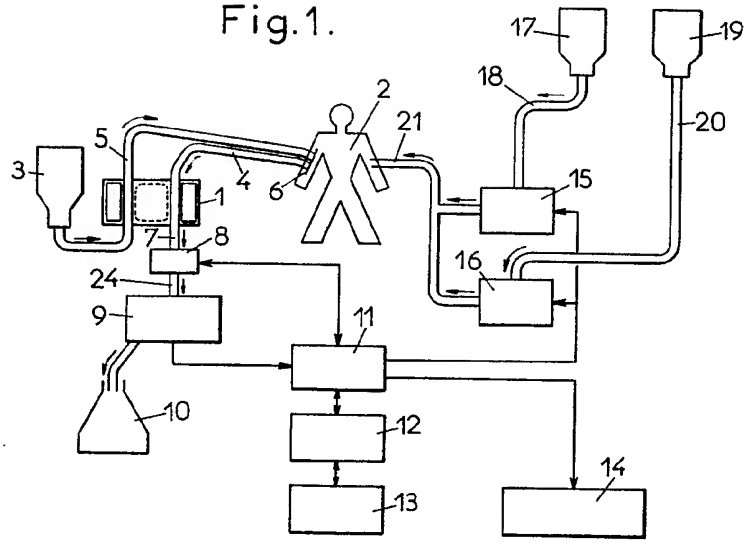


Fig.2.

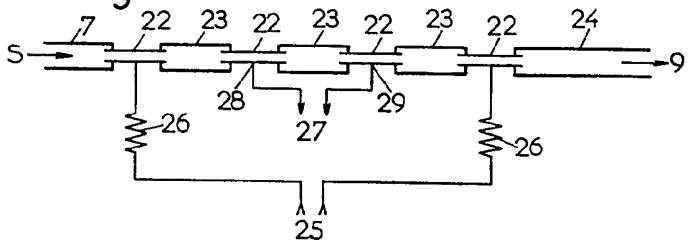
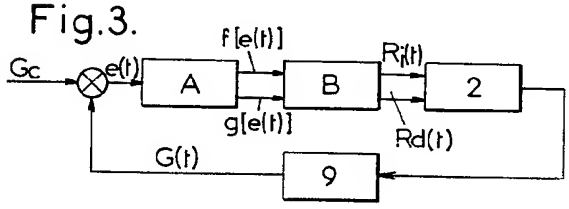


Fig.3.



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Sheet 2

Fig.4.